38. An adenovirus according to claim 36 wherein the E4 genes have been rendered non-functional by substitution of one or more bases in the E4 genes.

39. An adenovirus according to claim 38 wherein the E4 genes have been rendered non-functional by genetic modification(s) within regions responsible for the expression or transcriptional regulation, or both, whereby production of said genes is according to a desired mode of regulation.--

REMARKS

Claims 1-3, 6 and 9-39 are pending in the application. Claims 1, 9, 34 and 35 have been amended to reflect that E2 and E4 adenovirus regions contain a number of open reading frames, i.e. genes. Claim 10 has been amended to reflect that the L5 adenovirus region encodes the most rightward family of adenovirus late messenger RNAs processed from the major late unit. Support for the amended recitation of these claims is found in Examples 2, 3 and 6 of the specification. Claim 13 has been amended to correct a typographical error. Claim 21 has been amended to properly reflect lack of antecedent basis for the term "E4 gene".

Applicants have added claims 36-39. New claims 36-39 are supported by page 4, lines 6-15, page 9, lines 8-17 and page 10, lines 4-8 and 15 of the specification. Claim 37 is supported in addition by page 9, lines 26-33 of the specification.

No new matter has been added. All of the claims under consideration, as amended, are presented as an Appendix attached hereto.

CONCLUSION

Applicants respectfully request entry of the foregoing amendments and remarks in the file history of the instant application. In the event that a telephone interview would be helpful in advancing the prosecution of this application, Applicants' attorney invites the Examiner to contact the undersigned or Mr. Martin Savitzky at the number shown below.

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Respectfully submitted,

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APPENDIX
U.S. Patent Application Serial No. 08/397,225
"DEFECTIVE ADENOVIRUS VECTORS AND
USE THEREOF IN GENE THERAPY"
RPR File No. EX93015G1-US
Claims Under Consideration

1. (Four Times Amended) A defective recombinant adenovirus comprising

ITR sequences,
an encapsulation sequence, and
a heterologous DNA sequence,

wherein E1 genes have been rendered non-functional by deletion, and wherein E2 or E4 genes have been rendered non-functional by deletion.

2. (Twice Amended) An adenovirus according to claim 1, wherein adenovirus sequences are from a canine adenovirus.

3. (Thrice Amended) An adenovirus according to claim 1, wherein adenovirus sequences are from a human group C adenovirus.

6. (Thrice Amended) An adenovirus according to claim 1, wherein late genes L1-L5 have been rendered non-functional by deletion.

9. (Thrice Amended) An adenovirus according to claim 1, wherein E3 genes have been rendered non-functional by deletion.

10. (Thrice Amended) An adenovirus according to claim 9, wherein L5 has been rendered non-functional by deletion.

11. (Twice Amended) An adenovirus according to claim 1, further comprising a functional E3 gene under the control of a heterologous promoter.

12. (Thrice Amended) An adenovirus according to claim 1, wherein the heterologous DNA sequence is selected from the group consisting of therapeutic genes and genes encoding antigenic peptides.

13. (Four Times Amended) An adenovirus according to claim 12, wherein the heterologous DNA is a therapeutic gene which encodes a product selected from the group consisting of enzymes, blood proteins, hormones, lymphokines, growth factors, neurotrophic factors, apolipoproteins, dystrophin, minidystrophin, tumor suppressor genes, and coagulation factors.

14. (Twice Amended) An adenovirus according to claim 1, wherein the heterologous DNA encodes an antisense sequence.

15. (Twice Amended) An adenovirus according to claim 12, wherein the heterologous DNA encodes an antigenic peptide capable of generating an immune response against microorganisms, tumors, or viruses.

16. (Twice Amended) An adenovirus according to claim 15, wherein the gene encodes an antigenic peptide specific for a virus selected from the group consisting of the Epstein Barr virus, the HIV virus, the hepatitis B virus, and the pseudo-rabies virus.

17. (Twice Amended) An adenovirus according to claim 12, wherein the heterologous DNA sequence further comprises a promoter.

18. (Twice Amended) An adenovirus according to claim 12, wherein the heterologous DNA sequence further comprises a signal sequence.

19. (Twice Amended) A cell line comprising, integrated into its genome, the genes necessary to complement a defective recombinant adenovirus according to claim 1, wherein one of the complementing genes is under the control of an inducible promoter.

20. (Thrice Amended) A cell line according to claim 19, wherein it comprises, in its genome, an E1 gene and an E2 gene wherein the E2 gene is under the control of an inducible promoter.

21. (Thrice Amended) A cell line according to claim 20, wherein it additionally comprises an E4 gene from an adenovirus.

22. (Thrice Amended) A cell line according to claim 19, wherein it comprises, in its genome, an E1 gene and an E4 gene wherein the E4 gene is under the control of an inducible promoter.

23. (Twice Amended) A cell line according to claim 19, further comprising a glucocorticoid receptor gene.

24. (Thrice Amended) A cell line according to claim 19, wherein it comprises E2 and E4 genes and the E2 and E4 genes are under the control of an inducible promoter.

25. (Twice Amended) A cell line according to claim 19, wherein the inducible promoter is an LTR promoter of MMTV.

26. (Thrice Amended) A cell line according to claim 19, wherein it comprises a gene encoding the 72 K protein of E2.

27. (Twice Amended) A cell line according to claim 19, wherein it is obtained from the line 293.

28. (Twice Amended) A composition comprising a defective recombinant adenovirus according to claim 1 and a pharmaceutically acceptable vehicle.

29. (Twice Amended) A composition comprising a recombinant adenovirus according to claim 10 and a pharmaceutically acceptable vehicle.

30. (Twice Amended) A composition according to claim 28 wherein the vehicle is pharmaceutically acceptable for an injectable formulation.

31. (Twice Amended) A defective recombinant adenovirus comprising
ITR sequences,
an encapsulation sequence, and
a heterologous DNA sequence,
wherein E3 and E4 genes have been rendered non-functional by deletion.

32. (Amended) An adenovirus according to claim 31, wherein late genes L1-L5 have been rendered non-functional by deletion.

33. (Amended) A cell line according to claim 19, comprising open reading frames ORF6 and ORF6/7 of E4.

34. (Thrice Amended) A defective recombinant adenovirus consisting essentially of
ITR sequences,
an encapsulation sequence,
a heterologous DNA sequence, and
all or part of an E2 region,
wherein the E2 region or part thereof is the sole adenoviral gene.

35. (Thrice Amended) A defective recombinant adenovirus consisting essentially of
ITR sequences,
an encapsulation sequence,
a heterologous DNA sequence, and
all or part of an E4 region,
wherein the E4 region or part thereof is the sole adenoviral gene.

36. A defective recombinant adenovirus comprising
ITR sequences,
an encapsulation sequence, and
a heterologous DNA sequence,
wherein the E4 genes have been rendered non-functional.

37. An adenovirus according to claim 36, wherein the E4 genes have been rendered non-functional by deletion of all or part of the coding region, and/or all or part of the promoter region for E4 transcription.

38. An adenovirus according to claim 36 wherein the E4 genes have been rendered non-functional by substitution of one or more bases in the E4 genes.

39. An adenovirus according to claim 38 wherein the E4 genes have been rendered non-functional by genetic modification(s) within regions responsible for the expression and/or transcriptional regulation whereby production of said genes is according to a desired mode of regulation.